



MAIL STOP - PCT
Docket No.: 27577U

IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: DUNKERN, et al.

Art Unit: XX

Appl. No.: 10/590,992

Examiner: XX

Appl. Filing Date: August 29, 2006

Intl. Appl. No.: PCT/EP2005/050958

Intl. Appl. Filing Date: March 3, 2005

For: **NOVEL USE FOR PDE5 INHIBITORS**

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

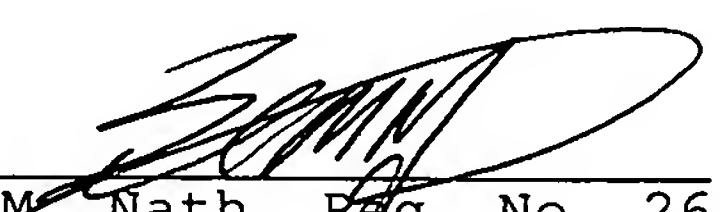
Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

1. Submission of Documents to Supplement Filing Documents under 35 USC 371; and
2. PCT/IPEA/409 (International Preliminary Report on Patentability) with 4 sheets of Annexes.

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account Number 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC

November 14, 2006


Gary M. Nath, Reg. No. 26,965
Sheldon M. McGee, Reg. No. 50,454
Customer No. 34375

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SUBMISSION OF DOCUMENTS
TO SUPPLEMENT FILING DOCUMENTS UNDER 35 USC 371

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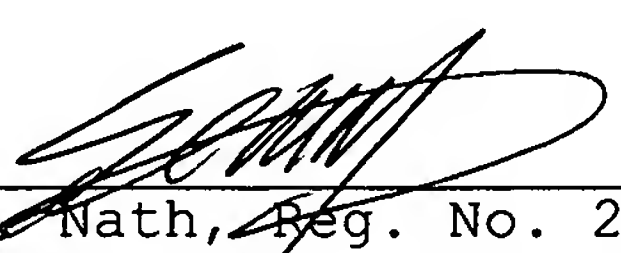
In order to supplement the filing documents for the national phase filing Under USC 371 commenced on August 29, 2006, applicant now submits the following documents:

1. PCT/IPEA/409 (International Preliminary Report on Patentability) with 4 sheets of Annexes.

Please charge any deficiency or credit any overpayment to our Deposit Account Number 14-0112.

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PATENT COOPERATION TREATY


Brigitte Kutter

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1169WOORD01		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2005/050958		International filing date (day/month/year) 03.03.2005		Priority date (day/month/year) 05.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/519 A61K31/53 A61K31/5025 A61P25/00				
Applicant ALTANA PHARMA AG				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 4 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 15.12.2005			Date of completion of this report 14.09.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465			Authorized officer Loher, Florian Telephone No. +49 89 2399-7839	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/050958

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-14 as published

Claims, Numbers

1-10 received on 15.12.2005 with letter of 14.12.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/050958

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5 (IA)

because:

- ☒ the said international application, or the said claims Nos. 1-5 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/050958

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	2, 7
	No: Claims	1, 3-6, 8-10
Industrial applicability (IA)	Yes: Claims	6-10
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: EP-A-1 317 924 (PFIZER LTD ;PFIZER (US)) 11 June 2003 (2003-06-11)
- D2: WO 02/089808 A (NIEWOEHNER ULRICH ;VAN DER STAAY FRANZ JOSEF (DE); HANING HELMUT () 14 November 2002 (2002-11-14)
- D3: WO 01/27112 A (BARBER CHRISTOPHER GORDON ;PFIZER LTD (GB); ALLERTON CHARLOTTE MOI) 19 April 2001 (2001-04-19)
- D4: EP-A-0 985 671 (MOCHIDA PHARM CO LTD) 15 March 2000 (2000-03-15)
- D5: WO 98/38168 A (TANABE SEIYAKU CO ;IKEO TOMIHIRO (JP); OMORI KENJI (JP); UKITA TAT) 3 September 1998 (1998-09-03)
- D6: ZHANG RUILAN ET AL: 'Nitric oxide enhances angiogenesis via the synthesis of vascular endothelial growth factor and cGMP after stroke in the rat.' CIRCULATION RESEARCH. UNITED STATES 21 FEB 2003, vol. 92, no. 3, 21 February 2003 (2003-02-21), pages 308-313, XP002279004 ISSN: 1524-4571

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Art 33(2) The subject-matter of claims 1-10 is new in the sense of Article 33(2) PCT. Prior art does not disclose a method or use as defined in present independent claims 1 and 6.

D1 discloses the use of PDE5 inhibitors, such as sildenafil vardenafil or tadalafil for the treatment of preeclampsia, stroke, Alzheimer's disease, cognitive impairment, Parkinson's and other degenerative disorders, which are diseases based on impairment or dysfunction of cerebral vascular reactivity as defined by the present application. D1 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

D2 discloses the use of PDE5 inhibitors, such as sildenafil for the treatment of dementia. Sildenafil is also used to treat cognitive disorders, vascular dementia, stroke and post-stroke dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis and Creutzfeld-Jacob disease. D2 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

D3 discloses the use of PDE5 inhibitors for the treatment of stroke, Alzheimer's disease and multiple sclerosis. D3 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

D4 discloses the use of PDE5 inhibitors for the treatment of cerebral circulatory disorders (e.g. cerebral infarction), brain dysfunction and dementia. D4 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

D5 discloses the use of PDE5 inhibitors for the treatment of cerebral hypofunction after cerebrovascular obstruction and cerebrovascular dementia. D5 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

D6 discloses the increase of post stroke angiogenesis after administration of sildenafil. The mechanism of action is inhibition of PDE5 and the consecutive

increase of cGMP. D6 does not disclose the use of said compounds in the treatment of diseases as defined by present claim 1 or 6.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1, 3-6 and 8-10 does not appear to involve an inventive step in the sense of Article 56 EPC.

D2 discloses the use of PDE5 inhibitors, such as sildenafil, for the treatment of diseases associated with the impairment or dysfunction of cerebral vascular reactivity, such as cognitive disorders, vascular dementia, stroke and post-stroke dementia.

The problem to be solved by the present invention may therefore be regarded as how to provide another therapeutic use of PDE5 inhibitors.

The present application suggests to solve the problem posed by using PDE5 inhibitors, in particular, sildenafil, vardenafil or tadalafil, for the treatment of diseases associated with the impairment or dysfunction of cerebral vascular reactivity as defined in present claims 1 or 6.

On a more abstract level the technical contribution to the state of the art suggested by the present application is a new medical use of known compounds. It must, thus, be of particular relevance that the compounds in question work over the whole range of the claimed use.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 1, 3-6 and 8-10 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person.

Being aware of the teaching of D1-D6 the selected diseases appear to be an arbitrary choice. Since there is no surprising effect resulting from that choice, the solution proposed in claims 1, 3-6 and 8-10 of the present application is not

considered to be inventive in the sense of Article 33(3) PCT.

The subject-matter of claims 2 and 7 seems to involve an inventive step in the sense of Article 33(3) PCT.

The wording of claims 2 and 7 suggests to solve the posed problem by using a PDE5 inhibitor for the treatment of sepsis associated encephalopathy (SAE).

There is no hint in the prior art to use PDE5 inhibitors in the treatment of SAE.

The present application provides *in vivo* data demonstrating that administration of a PDE5 inhibitor in a LPS-treated rat has an effect on cerebral blood flow and SEP amplitude, suggesting its efficacy in the treatment of SAE.

Therefore, the solution proposed by claims 2 and 7 of the present application solves the posed problem and is considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 1-5 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 6-10 is considered to be industrially applicable in the sense of Art 33(4) PCT.

PCT/EP2005/050958

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WO 2005/089766

December 14, 2005

Amended set of claims

1. A method of treatment or prophylaxis of a disease associated with or based on impairment or dysfunction of cerebral vascular reactivity selected from the group of sepsis associated encephalopathy, sepsis, toxic encephalopathy, encephalopathy associated with autoimmune thyroiditis, autoimmune thyroiditis, cerebral microangiopathy, hypercholesterolemia and hypertriglyceridemia in a patient afflicted with such disease comprising the step of administering a pharmacologically tolerable and therapeutically effective amount of a PDE5 inhibitor to the patient.
2. A method according to claim 1, wherein the disease is sepsis associated encephalopathy.
3. A method according to claim 1 or 2, wherein the PDE5 inhibitor is selected from the group of 3-ethyl-8-[2-(4-morpholinylmethyl)benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione, 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide, 9-bromo-2-(3-hydroxypropoxy)-5-(3-pyridylmethyl)-4H-pyrido[3,2,1-jk]-carbazol-4-one, 4-(1,3-benzodioxol-5-ylmethylamino)-2-(1-imidazolyl)-6-methylthieno[2,3-d]pyrimidine, 6-(2-isopropyl-4,5,6,7-terahydropyrazolo[1,5-a]pyridin-3-yl)-5-methyl-5-methyl-2,3,4,5-tetrahydropyridazin-3-one, 5-(4-methylbenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-pyridin-4-ylmethyl-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(4-bromobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-benzyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(3,4-dimethoxybenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo-[4,5-d]pyrimidin-7-one, 5-(3,4-dichlorobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-biphenyl-4-ylmethyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(4-aminobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(hydroxyphenylmethyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo-[4,5-d]pyrimidin-7-one, 5-benzo[1,3]dioxol-5-ylmethyl-3-[1-methyl-4-phenylbutyl]-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, N-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo-[4,5-d]pyrimidin-5-ylmethyl]phenylacetamide, 5-benzoyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]-pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-[4-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-[3-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro[1,2,3]triazolo[4,5-d]pyrimidin-7-one, N-methyl-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]-triazolo-[4,5-d]pyrimidin-5-ylmethyl]-benzenesulphonamide, N-(2-dimethylaminoethyl)-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-

ylmethyl]benzenesulphonamide, N-(2-hydroxyethyl)-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonamide, ethyl 1-[3-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]-triazolo-[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonyl]piperidinecarboxylate, 3-(1-methyl-4-phenylbutyl)-5-[4-(4-methylpiperazin-1-sulphonyl)benzyl]-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-benzo[1,3]dioxol-5-ylmethyl-3-[1-ethy-heptyl]-3,6-dihydro-[1,2,3]-triazolo[4,5-d]pyrimidin-7-one, 3-[1-(1-hydroxyethyl)-4-phenylbutyl]-5-[4-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furanmethanol, 1-benzyl-6-fluoro-3-[5-(hydroxymethyl)furan-2-yl]-1H-indazole, 2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)quinazoline, 1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulphonyl]-4-methylpiperazine, 4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)phthalazine-6-carbonitrile, 1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]piperidin-4-carboxylic acid, (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-1,2,3,4,6,7,12,12a-octa-hydropyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (tadalafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, 4-ethoxy-2-phenylcycloheptylimidazole, (6-bromo-3-methoxymethylimidazo[1,2-a]pyrazin-8-yl)methylamine, 8-[(phenylmethyl)thio]-4-(1-morpholinyl)-2-(1-piperazinyl)pyrimidino[4,5-d]pyrimidine, (+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one, cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one, 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, 2-(2-propoxyphenyl)purin-6(1H)-one, 2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one, methyl 2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro-[2,7]naphthyridin-3-carboxylate, methyl 2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylate, 2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one (vardenafil), 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone (vesnarinone), 1-cyclopentyl-3-methyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one, 1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one, 6-o-propoxyphenyl-8-azapurin-6-one, 3,6-dihydro-5-(o-propoxyphenyl)-7H-v-triazolo[4,5-d]pyrimidin-7-one and 4-methyl-5-(4-pyridinyl)thiazole-2-carboxamide and the pharmaceutically acceptable derivatives of these compounds.

4. A method according to claim 3, wherein the PDE5 inhibitor is selected from the group of sildenafil, vardenafil, tadalafil, a pharmaceutically acceptable salt thereof and a solvate of the pharmaceutically acceptable salt thereof.

5. A method according to claim 4, wherein the PDE5 inhibitor is selected from the group of sildenafil citrate, vardenafil hydrochloride, the trihydrate of vardenafil hydrochloride and vardenafil dihydrochloride.
6. Use of a PDE5 inhibitor in the manufacture of a medicament for the treatment or prophylaxis of a disease associated with or based on impairment or dysfunction of cerebral vascular reactivity selected from the group of sepsis associated encephalopathy, sepsis, toxic encephalopathy, encephalopathy associated with autoimmune thyroiditis, autoimmune thyroiditis, cerebral microangiopathy, hypercholesterolemia and hypertriglyceridemia.
7. Use according to claim 6, wherein the disease is sepsis associated encephalopathy.
8. Use according to claim 6 or 7, wherein the PDE5 inhibitor is selected from the group of 3-ethyl-8-[2-(4-morpholinylmethyl)benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione, 1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide, 9-bromo-2-(3-hydroxypropoxy)-5-(3-pyridylmethyl)-4H-pyrido[3,2,1-jk]-carbazol-4-one, 4-(1,3-benzodioxol-5-ylmethylamino)-2-(1-imidazolyl)-6-methylthieno[2,3-d]pyrimidine, 6-(2-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-5-methyl-5-methyl-2,3,4,5-tetrahydropyridazin-3-one, 5-(4-methylbenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-pyridin-4-ylmethyl-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(4-bromobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-benzyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(3,4-dimethoxybenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(3,4-dichlorobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-biphenyl-4-ylmethyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(4-aminobenzyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-(hydroxyphenylmethyl)-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-benzo[1,3]dioxol-5-ylmethyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, N-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]phenylacetamide, 5-benzoyl-3-(1-methyl-4-phenylbutyl)-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-[4-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 3-(1-methyl-4-phenylbutyl)-5-[3-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro[1,2,3]triazolo[4,5-d]pyrimidin-7-one, N-methyl-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonamide, N-(2-dimethylaminoethyl)-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonamide, N-(2-hydroxyethyl)-4-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonamide, ethyl 1-[3-[3-(1-methyl-4-phenylbutyl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylmethyl]benzenesulphonyl]piperidinecarboxylate, 3-(1-methyl-4-phenylbutyl)-5-[4-(4-methylpiperazin-1-sulphonyl)benzyl]-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one,

5-benzo[1,3]dioxol-5-ylmethyl-3-[1-ethy-heptyl]-3,6-dihydro-[1,2,3]-triazolo[4,5-d]pyrimidin-7-one, 3-[1-(1-hydroxyethyl)-4-phenylbutyl]-5-[4-(morpholine-4-sulphonyl)benzyl]-3,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one, 5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furanmethanol, 1-benzyl-6-fluoro-3-[5-(hydroxymethyl)furan-2-yl]-1H-indazole, 2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)quinazoline, 1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulphonyl]-4-methylpiperazine, 4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)phthalazine-6-carbonitrile, 1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]piperidin-4-carboxylic acid, (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-1,2,3,4,6,7,12,12a-octa-hydropyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (tadalafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, 4-ethoxy-2-phenylcycloheptylimidazole, (6-bromo-3-methoxymethylimidazo[1,2-a]pyrazin-8-yl)methylamine, 8-[(phenylmethyl)thio]-4-(1-morpholinyl)-2-(1-piperazinyl)pyrimidino[4,5-d]pyrimidine, (+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one, cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one, 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, 2-(2-propoxyphenyl)purin-6(1H)-one, 2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one, methyl 2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro-[2,7]naphthyridin-3-carboxylate, methyl 2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylate, 2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one (vardenafil), 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone (vesnarinone), 1-cyclopentyl-3-methyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one, 1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one, 6-o-propoxyphenyl-8-azapurin-6-one, 3,6-dihydro-5-(o-propoxyphenyl)-7H-v-triazolo[4,5-d]pyrimidin-7-one and 4-methyl-5-(4-pyridinyl)thiazole-2-carboxamide and the pharmaceutically acceptable derivatives of these compounds.

9. Use according to claim 8, wherein the PDE5 inhibitor is selected from the group of sildenafil, vardenafil, tadalafil, a pharmaceutically acceptable salt thereof and a solvate of the pharmaceutically acceptable salt thereof.
10. Use according to claim 9, wherein the PDE5 inhibitor is selected from the group of sildenafil citrate, vardenafil hydrochloride, the trihydrate of vardenafil hydrochloride and vardenafil dihydrochloride.